

Dr. Ch. Heusser

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Declaration of Christoph H. Heusser

I, Christoph H. Heusser, declare:

1) I am a senior scientist at Ciba-Geigy Ltd, Basel. I was nominated Ciba Fellow in 1994. I am an immunologist and project leader, responsible for immunology based projects in the indication Asthma /Allergy. I studied biochemistry and specialized in immunology (PhD from Swiss Federal Institute of Technology, Zürich) and was a member at the Basel Institute for Immunology before joining Ciba in 1979. I am familiar with the design and production of recombinant antibodies. Annex I to this declaration is my CV.

2) This is to testify to my relationship with Prof. M. Shulman and my collaboration and interaction with him particularly during the time from November 1982 to March 1983 and to testify to the status of Prof. M. Shulman's work and our knowledge, concept, and technical capability for the generation of chimeric human-mouse recombinant antibodies at that time.

3) In the period from 1976 to 1979 when I was working as a member at the Basel Institute for Immunology, I was collaborating with Marc Shulman and George Köhler in the context of generating new monoclonal antibody (mAb) producing hybridomas. Initially, Marc was involved in refining the method of generating mAb (i.e. selection of fusion partner cell lines which would not produce mAb themselves but support the expression of antibody, allowing for the selective expression of the antibody of interest and in a pure form) and later in the selection of antibodies with altered properties.

4) I joined Ciba-Geigy in October 1979, and was involved in research on the regulation of antibody responses. In this context I maintained my collaboration with Marc who had moved to Toronto. We were interested in investigating if a B cell hybridoma could make variants of an original antibody. In mutation experiments we were able to select hybridomas which expressed various variant antibodies (for example only F(ab) fragments of domain deletions - M. Shulman, Ch. Heusser, C. Filkin, G. Köhler, Mol. Cell. Biol. 1033, 1982). This work showed that altered antibody genes could be functionally expressed.

5) In 1982 Marc worked on methods for transfer and expression of antibody gene constructs in hybridoma cells. Work done in collaboration with N. Hozumi and colleagues showed that the cloned Ig DNA of an antibody light chain gene contained sufficient information to be well expressed when transferred to hybridoma cells (the work on the kappa light chain gene was published as Ochi *et al*, Nature 302: 340, 1983).

6) On November 19, 1982 Marc was visiting me in Ciba-Geigy Basel, and we were sitting in the Ciba-Geigy Canteen when Marc referred to the work of inserting antibody genes into a cell line for functional expression of that antibody (he had just submitted the Ochi *et al*. manuscript to Nature). Marc said that he could now make any antibody I would like. We returned to my office. In answer to Marc's statement, I proposed to make antibodies with V regions derived from the mouse and C regions from humans for use in therapeutic applications. He considered this a very good idea. We decided to create such an antibody in collaboration.

8) Marc designed a way to assemble the separate mouse V and human C DNA constructs using well established DNA manipulation techniques, from gene constructs which were then available to him. V_{mouse} - C_{human} constructs could then be introduced into pSV2-neo plasmids (P. Southern and P. Berg, J. Mol. Appl. Gent. 1: 327 - 341, 1982) for expansion in bacteria and expression of antibodies in specific non-producer mammalian myeloma cells after protoplast according to published information, similar to the procedure that Marc had already used for the TNP-light chain transfection (Ochi *et al*.)

9) In the following period we intensified our communication, mainly by phone, and in December 1982 Marc and his student G. Boulianne had already excised the gene fragments for assembling the chimeric constructs (see letter from December 12, 1982 from Marc to me (Annex 2)). The assembly used standard DNA manipulation procedures which were state of the art at that time. In this letter he indicated to me that he expected to test the function of these genes by cell transfection within a few weeks.

10) In the meantime I had discussions with various persons within Ciba-Geigy regarding the goal of generating human-mouse chimeric antibodies as potential therapeutics. These discussion partners included the head of department Prof. D.G. Braun (contacted on November 23, 1982) and the head of Biology, Dr. P. Dukor (discussion on the November 25, 1982) who both were very excited about the plan and assured me of full support. By the end of 1982, therefore, Ciba-Geigy AG had initiated an official project for the generation of chimeric antibodies in non-producer mammalian myeloma cells.

11) Marc later published his work on chimeric antibodies in Nature (G. Boulianne N. Hozumi, & M. Shulman, Nature 312: 643, 1984) which was one of the three original descriptions of chimeric antibodies all of which appeared around the same time (late 1984). In this publication my contribution to the conception of this work is acknowledged at the bottom of page 645.

Signed this 21 day of May, 1996



Christoph H. Heusser

CURRICULUM VITAE

Name: Christoph H. HEUSSER

Date of birth: November 29th, 1944

Nationality: Swiss

Citizenship and place of birth: Zürich (Switzerland)

Marital status: Married: two children

Address:	Business:	CIBA-GEIGY Limited Allergy/Immunology Res. Phone: 061-697 54 89 R-1056.4.09 FAX: 061-697 88 56 4002 <u>Basel</u> , Switzerland
	Private:	Hafenrainstr. 21 4104 <u>Oberwil</u> , Phone: 061-401 20 03 Switzerland

Present: Head of Immunoregulation Projects:
Project Leader of "IgE Regulation", "TH2(IL-4/5) cytokine Inhibition",
"Anti-IgE Antibodies", and "Stat-6 Inhibition"
Asthma/Allergy/Immunology, Research,
Ciba-Geigy Limited, Basel

Appointments and Education:

1979-present: CIBA-GEIGY LTD.

Head of the Immunoregulation Research at the Pharmaceuticals Research Division.

Main domain of research and Project leader: Immun regulation in allergy and asthma:

Regulation of IgE isotype production by B cells and cytokine production by T cells as well as IL-4 signalling.

Further activities: Generation of monoclonal antibodies for diagnostic and therapeutic purposes.

1994 nominated Ciba-Fellow

1992 appointed as "Scientific Expert" of CIBA-GEIGY

1990 appointed as scientific "Research Specialist" of CIBA-GEIGY

1982-1986 Head of section Immunology; 1984 Handlungsbevollmächtigter, CIBA-GEIGY LTD.

1976-1979: Basel Institute of Immunology, Basel, Members and research scientist:

Domain of research: Mechanism of B cell development and immune regulation by anti-idiotypic antibodies.

1974-1976: Denver Medical Center, USA.

Dept. of Medicine Section Allergy and Clinical Immunology of the National Jewish Hospital and Research Center; postdoctoral fellow and research collaborator.

Domain of research: Structural and functional characterization of Fc receptors on B and T lymphocytes and macrophages. Sponsor: Prof. Dr. H. Grey (M.D.)

Stipend: Fellowship for young investigators of the Swiss National Foundation for Scientific Research.

1969-1974: Institute of Biochemistry, University of Lausanne

(and Swiss Institute for Cancer Research, Lausanne). Research collaborator, doctoral candidate, and assistant for biochemical laboratory teaching.

Director of thesis: Prof. Dr. H. Isliker. Domain of research: Structural functional relationship of the human component complement C1q.

Immatriculation of thesis: Swiss Federal Institute of Technology, Zürich. Degree: Dr. sc. nat. ETH (Ph.D.)

1964-1969 Swiss Federal Institute of Technology, Zürich.

Faculty of Natural Science in chemical-biological-microbiological section, specialized in biochemistry.

Sponsor: Prof. Dr. C. Martius. Degree: Master in biochemistry (dipl. sc. nat. ETH).

Elected Memberships:

- Member of the European Academy of Allergy and Clinical Immunology
- Member of the Collegium Internationale Allergologicum

Society Memberships:

- Swiss Society for Allergy and Immunology.
- American Association of Immunologists.
- German Society for Immunology.
- Swiss Society for Biochemistry.

Special Functions:

- Member of the board of the Swiss Institute of Allergy and Asthma Research, Davos

Main International Conference Lectures and Chairmanships:

- Chairman of various symposia and workshops at international meetings (e.g. chairman of symposium on "IgE-Regulation", International Conference for Immunology, Berlin, 1989).
- Organizer of various symposia at international conferences
- Invited speaker for several plenary lectures at international meetings, most recent once:
 - Collegium International Allergologicum, Madeira, 1991.
 - European Congress for Allergy and Clinical Immunology, Zürich 1991.
 - Meeting of the British Society for Allergy and Clinical Immunology, London, 1991.
 - European Conference for Allergy and Clinical Immunology, Paris, 1992.
 - International Paul Ehrlich Seminar, Langen, 1993.
 - Intern. Symp. Mol. Biol. Allergens and Atopic Immune Response, Quebec City, 1995
 - European Respiratory Society, Stockholm, 1996

Journal Referee (ad hoc):

- Clinical and Experimental Allergy
- Cytokine
- European Journal of Immunol.
- Int. Arch. Allergy Appl. Immunol.
- International Immunology
- Journal of Immunology
- Molecular Immunology

Teaching experience at Universities:

- Lectures in Immunology for Ph.D. students at University of Bern and Zürich (1981-1990)-
- Lectures at the yearly Swiss Postgraduate Courses in Experimental Medicine (1984-present).
- Laboratory teaching: Experiments on humoral immune responses and immunological methods (for students in medicine and science) .

Languages:

- German (mother tongue)
- English
- French

Scientific References:

- Prof. H.Isliker, Inst. of Biochem. and ISREC, Epalinges, Switzerland.
- Prof. H.Grey, Vice President of Cytel, La Jolla, California.
- Prof. R.Gisler, and Prof. F.Melchers, Basel Institute for Immunology, Basel, Switzerland.
- Dr. P.Dukor, Sandoz Research Institute, Vienna, Austria
- Prof. G.Delespesse, University of Montreal, Notre Dame Research Center, Montreal, Canada.
- Dr.R.Paioni and Prof. T.Staehelin, Research Department, CIBA-GEIGY Ltd., Basel, Switzerland.